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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SINGH, ANOOP KUMAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,028	BRAHMBHATT ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-15 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-15 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/29/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed September 17, 2009 have been fully considered but they are not persuasive. Claim 8 has been amended, while claims 1-7, 9, 16, 23-29 and 30 have been canceled. Currently, claims 8, 10-15, 17-21 and 22 are pending.

Election/Restrictions

Applicants' election without traverse of claims 8-33 and 38 (Group II) in the reply filed on January 15, 2009 was acknowledged.

Claims 8, 10-15, 17-21 and 22 drawn to a targeted drug delivery method are under examination.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 8, 10-12, 15, 17-19, 21 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002).

The bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively.

With respect to claims 8, 10-12, Sabbadini et al. teach a targeted drug delivery method comprising contacting a target non-phagocytic mammalian cell with an intact bacterially derived minicell coated with an antibody as a binding moiety capable of binding to a ligand present on

the surface of the target mammalian cell, wherein the minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-15, col. 7, lines 10-15, col. 136, lines 58-66 , table 9 and claim 1). It is noted that Sabbadini et al disclose mammalian cell surface display receptor such as EGFR that is capable of activating receptor mediated endocytosis with minicell (see example 19). Sabbadini et al also teach contacting target non-phagocytic tumor cells with intact minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). Sabbadini et al. also teach that the minicells of the invention are capable of encapsulating and/or loading into a membrane a variety of substances that includes small molecules (see column 161, lines 37-46, column 17, line 16). Sabbadini et al teach that the minicells are engulfed by cells by a process such as receptor mediated endocytosis (see col. 171, line 55). Additionally, it is also disclosed that the method results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Sabbadini et al disclose that the target mammalian cell may include A-431 cancer cell lines that are non phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that the cell displays a ligand specifically recognized by a binding moiety attached to the minicell. The moiety to be conjugated to the minicells can be a polypeptide (limitation of claim10). It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66), which binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively (limitation of claims 11 and 15). Sabbadini et al also teach minicell comprising a therapeutic agent displays a binding moiety such as antibody that specifically binds a receptor present on the surface of a non phagocytic cell meeting the limitation of first and second arm being monospecific (col. 7, lines 6-15, limitation of claim 12). Sabbadini et al teach that the antibody may be a single chain antibody (see col. 132, line 60) or a humanized antibody (col. 132, line 53) (limitation of claims 17 -18). With respect to claims 19 and 24, Sabbadini et al disclose that the minicells produced contains an intact cell wall (see col. 39, lines 34-35, and claims 1, 8 in '105).

With respect to claims 21-22, 26-27, Sabbadini et al. teach that method of targeted drug delivery using minicell can be carried out under *in vitro* or *in vivo* condition (see col. column 11, line 14 and col. 36, lines 56-59). Accordingly, Sabbadini et al. anticipates claims 8, 10-12, 15, 17-19, 21-22.

Response to arguments

Applicant arguments filed September 17, 2009 have been fully considered but are found not persuasive. Applicants' cancellation of claims 9, 16, 23-29 and 30 renders their rejections moot. Applicants disagree with the rejection of claims and argue that Sabbadini present broad genus of cell types, including eubacterial minicell, eukaryotic minicell and anchebacterial minicell and characterization of minicell as useful for delivering "genus of therapeutic agents" including small molecule, polypeptide, antibodies, nucleic acid and drugs . Applicants assert that Sabbadini do not delineate "targeted drug delivery method, bispecific ligand having specificity for a mammalian cell surface receptor capable of activating receptor-mediated endocytosis" and small drug molecule (see pages 5 and 6 of the arguments).

Applicants' arguments have been fully considered, but are not found persuasive. As an initial matter, base claim is directed to a targeted drug delivery method that involves one active method step comprising bringing bispecific ligands having specificity for a mammalian cell surface receptor capable of activating receptor mediated endoytosis into contact with (a) intact bacterially derived minicell that contains small drug molecule and (b) non-phagocytic mammalian cell. Contrary to applicant's arguments that disclosure of Sabbadini et al is cherry picking elements from a laundry list, it is noted that Sabbadini et al. specifically teaches the method of bringing a target non-phagocytic mammalian cell with a minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of the target mammalian cell, wherein the bacterially derived intact minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-15, col. 7, lines 10-15, col. 136, lines 58-66). Sabbadini et al specifically teach using bacterially derived intact minicells that contain 1 contaminating parent bacterial cell per 10^7 minicells (see Table 9, col. 234), therefore such a preparation of isolated intact minicells disclosed by Sabbadini et al is interpreted free of any contaminant. In view of foregoing it is

clear that Sabbadini teaches the use of isolated minicells for delivery of small molecules , wherein isolated intact purified minicell is free of contaminants (table 9, example 17 and claim 1) and thus would anticipate the claimed invention.

With regard to applicants' argument that Sabbadini et al fail to teach bringing bispecific ligand into contact with any minicell (see page 6, para. 30, it should be noted that bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively. In this regard, contrary to applicants' assertions, Sabbadini et al teach contacting a mammalian cell with a bacterial minicells comprising a therapeutic agent that is coated with an antibody as a binding moiety that specifically binds a ligand present on the surface of said mammalian cell such that the contents of the minicells are delivered into the cell from a minicell bound to the cell. It should be noted that the antibody is covalently attached as a binding moiety (see column 136, lines 58-66) that binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand disclosed by Sabbadini et al comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively (limitation of claims 11 and 15).

With regard to applicants' argument that Sabbadini et al teach use of plurality of different minicell and therapeutic agents, it should be noted that the disclosure of other embodiments in Sabbadini et al does not negate the fact that cited art specifically teaches the claimed elements. Applicants have not provided any evidence on record as to why the delivery of other molecules are not enabling. The claimed composition in the method appears to be structurally and functionally similar.

Applicants argue that the teachings of Sabbadini are not well-delineated (see page 6). , Applicants further argue that conventional wisdom held that large particles like intact bacterially derived could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis (see page 7). Applicants cite the reference of Nettelbeck *et al.,* 2001 and Boucher *et al.,* 2003 to assert that the clathrin-coated pits resemble a cup that envelopes the vector, but the size of the cup is understood to be a limiting factor. Clathrin-coated pits have a limited size of

85-110 nm, due to the size of the clathrin coat. Applicants cite Swanson & Watts, 1995 to support the assertion that minicells are at least 400 nm in diameter. Hence, the skilled artisan would not have expected this targeting approach to work for minicells. Applicants further argue that specific investigations into the effect of particle size on receptor-mediated endocytosis showed the process to be strongly size-dependent (see Aoyama *et al.,* 2003, Nakai *et al.,* 2003; Osaki *et al.,* 2004. Gao *et al.,* 2005) (see page 8 of the argument).

In response, it is noted that like instant specification, Sabbadini et al teach an isolated minicell that is broadly interpreted to be a purified minicell free of contaminants capable of delivery of molecules to a target cells. Sabbadini et al teaches same method steps as claimed using similar composition. Applicants should noted that Sabbadini et al teach contacting target non-phagocytic tumor cells with minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). Additionally, it is also disclosed that the method results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Furthermore, tumor cells disclosed by Sabbadini et al meets the structural limitations of "a mammalian cell surface capable of activating receptor mediated endocytosis" "because it is capable of providing the intended use limitation "receptor mediated endocytosis ". In response to applicant's argument that large particles like intact bacterially derived could not passively enter non-phagocytic mammalian cells via receptor-mediated endocytosis, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, and then it meets the claim. One of ordinary skill in the art based on the teachings of the specification would conclude that the target non-phagocytic cells disclosed in the method of Sabbadini et al would serve the purpose as claimed.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., size of minicell diameter) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Applicants may wish to amend the claims to limit the bacterially derived intact minicells to a "specific size" in order to distinguish minicells of claimed method from the one known in prior art.Applicants further argues that Sabbadini, in the cited section on "Cancer Therapy", suggests that macrophages are required to accomplish receptor-mediated endocytosis and that for direct access into target cells, expression of a toxR-invasin fusion protein might be used to an actively induce entry. Applicants also assert that Sabbadini contemplated using protoplast.(See column 171, line 53 to column 172, line 3 and example 19, argument page 8).

Such is found not persuasive because the applicants' fails to provide any evidence that sufficiently support this assertion. Applicants have further engaged in selective reading of the teachings of Sabbadini et al. to formulate the grounds for not teaching the non-phagocytic cells. Contrary to applicants' assertion Sabbadini et al teach tumor cells that are engulfed by isolated minicells by receptor mediated endocytosis in a manner similar to one with macrophage (for example). Furthermore, human cancer cells (A431 cells) are known to be non-phagocytic. Additionally, it is known in prior art that all mammalian cells are endocytosis-competent and thus would also be inherent in the human cancer cells taught by Sabbadini. In fact, Sabbadini et al teach contacting target non-phagocytic tumor cells with minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). MPEP 2164.01[R5] states "[A]ny part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein. In the instant case, Sabbadini teach the claimed method step and also disclose method to isolate composition "containing fewer than about 1 contaminating parent bacterial cell per 10^7 minicells" (see Table 9, col. 234) and such a preparation of minicells disclosed by Sabbadini et al was generally free of any contaminant.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 11, 13-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957).

With respect to claims 8, 11, Sabbadini et al. teach a targeted drug delivery method comprising contacting a mammalian cell with minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of said mammalian cell, wherein the minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-15, col. 7, lines 10-15, col. 136, lines 58-66). Sabbadini et al. also teach that the minicells of the invention are capable of encapsulating and/or loading into a membrane a variety of substances that includes small molecules (see column 161, lines 37-46, column 17, line 16). Sabbadini et al teach that the minicells are engulfed by cells by a process such as receptor mediated endocytosis (see col. 171, line 55). Additionally, the method disclosed by Sabbadini et al results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Sabbadini et al disclose that the target mammalian cell may include cos and A-431 cancer cell line that are non phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66), which binds to ligand present on the surface of a mammalian cell. Although, Sabbadini et al. teach a method of drug delivery by covalently attaching binding moieties such as antibody to minicells such that it binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that the first arm specific to an O-polysaccharide component of LPS or first and second arm are multivalent.

However, prior to instant invention, Nettelbeck et al teach a recombinant antibody as a molecular bridge, linking the virus capsid to the endothelial cell surface protein endoglin, for vascular targeting of adenoviruses (abstract). It is noted that Nettelbeck et al also disclose a method to construct bispecific single chain multivalent antibody directed against endoglin and the adenovirus knob domain (see 885, col.1, para.4). It is also disclosed that the ScFv C4 (endoglin) and the neutralizing anti-knob scFv S11 are combined in a bispecific single-chain diabody (scDb EDG-Ad) (see figure 3) for experimental analysis. Nettelbeck et al reported enhanced oviral infectivity mediated by scDb EDG-Ad that was restricted to endoglin-positive cells showing cell specific targeting (see figure 6, page 889, col. 2, para. 2).

Although Nettelbeck et al describes the advantage of using bispecific diabody to target viral fiber knob domain to endoglin expressing cancer cell, but differed from claimed invention by not disclosing first arm specific to an O-polysaccharide of a LPS.

Prior to instant invention, Coldwell et al teach production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide (LPS) (abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Nettelbeck et al and Coldwell by using an antibody to bring together intact minicell and mammalian cell such that minicell binds to mammalian cell and minicell that are engulfed by the mammalian cell with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to use an single chain antibody diabody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for targeted delivery of small moelcule by attaching an antibody to a bacterial minicells that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those in Nettelbeck and Coldwell would have resulted in specific small molecule transfer into endoglin positive endothelial cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 8, 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002) and Hope et al (WO/1996/026715, dated 06/09/1996, IDS)

With respect to claims 8, 23, Sabbadini et al. teach a targeted drug delivery method comprising contacting a mammalian cell with minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of said mammalian cell, wherein the minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-16, col. 7, lines 10-15, col. 136, lines 58-66). Sabbadini et al. also teach that the minicells of the invention are capable of encapsulating and/or loading into a membrane a variety of substances including small molecules and antibiotics (see column 161, lines 37-46). It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66), which binds to ligand present on the surface of a mammalian cell. Sabbadini et al also teach that minicells are engulfed by the cell by receptor mediated endocytosis (see column 171, col. 1, line 62-65). Regarding claim 23, Sabbadini et al also teach contacting target tumor cells with minicells containing toxic drug molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by phagocytosis or receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65).

Although, Sabbadini et al. teach a method of drug delivery by covalently attaching an antibody to minicells capable of encapsulating into a membrane small molecules such that

antibody at the surface of minicell binds to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not teaching encapsulation of a chemotherapeutic agent.

However, prior to instant invention, it was routine in the art to package/load chemotherapeutic drugs such that diffusion across the phospholipid bilayer-membrane is unidirectional for targeted delivery of the molecule. For instance, Hope et al teach a method a method involves loading a chemotherapeutic agent such as doxorubicin into preformed lipid bilayer of liposome having a concentration gradient across the lipid bilayer (see Figure 1). It is noted that Hope et al disclose that the structure of the lipid bilayer is similar to the membranes enveloping animal cells (see page 1, line 21).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Hope by modifying the method of targeted drug delivery of Sabbadini et al by loading chemotherapeutic agent such as doxorubicin into minicell using the method disclosed by Hope with a reasonable expectation of achieving predictable result. A person of skill in the art would have been motivated to encapsulate doxorubicin into the minicell because Sabbadini et al embraced the potential of delivering cytotoxic agent specifically to the tumor for cancer therapy (supra). One who would have practiced the invention would have had reasonable expectation of success since Hope had already taught a method for loading doxorubicin in a preformed lipid bilayer having a concentration gradient across the lipid bilayer, while Sabbadini et al disclosed that cellular membrane of the minicell is a lipid bilayer that forms the boundary between the interior of a cell and its external environment. Thus, it would have required routine experimentation for one of ordinary skill in the art to combine the teachings of Sabbadini et al with those of Hope to load doxorubicin or any other acidic or basic chemo therapeutic in the minicell for targeted drug delivery to enhance the therapeutic effect.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

Applicant arguments filed September 17, 2009 have been fully considered but are found not persuasive. Applicant's arguments all rely on the teaching of Sabbadini et al that have been discussed in the preceding section. Applicants argue that it was surprising that intact minicell membranes are permeable to a range of structurally dissimilar hydrophilic, hydrophobic and amphipatic drugs (see page 9 of the arguments). Applicants further assert that it was unexpected that therapeutically significant concentrations of drug could be packaged within minicells. Applicants also assert that the ability of minicells to deliver drugs also was surprising. It was unexpected, for example, that drug-packaged minicells do not leak drug into the extracellular space.

Such is found not persuasive because unexpected results have to be commensurate with the scope of the invention. "Whether the unexpected results are the result of unexpectedly

improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." Thus, the scope of the claims is not commensurate with the unexpected result (therapeutically significant concentrations of drug or any therapeutic effect). The claims are not limited to therapeutically significant concentrations of drug or any therapeutic effect and therefore the issue is whether prior art teaches necessary element so that one of ordinary skill in the art would have combined the teaching to achieve predictable results of delivering drug by bringing intact minicell containing small molecule drug and target non-phagocytic mammalian cells. Additionally, with respect to applicants' submission that it was unexpected to deliver therapeutically significant concentrations of drug and the ability of minicells to deliver drugs and destabilization of minicell integrity, it is emphasized that the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that the specific limitations and conditions as set forth in argument is *effective* in delivering the drug to a target cells. A person of skill in the art would have been motivated to use an single chain antibody diabody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for targeted delivery of small moelcule by attaching an antibody to a bacterial minicells that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those in Nettelbeck and Coldwell would have resulted in specific small molecule transfer into endoglin positive target mammalian cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 8, 16, 19-22 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40-44, 48-51 and 73 of copending Application No. 11/765635. It is noted that Applicant has requested that the rejection be held in abeyance until allowable subject matter can be identified, a request of abeyance does not overcome or address an issue of obvious double patenting between claims 8, 16, 19-22 in the instant case and application 11/765635. Therefore, the rejection is maintained for the reasons of record.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tomlinson I et al (.Methods Enzymol, 2000, 326, 461-479) teach a method for generating multivalent and bispecific antibody fragments.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Anoop Singh
AU 1632